An Operational Perspective of Challenging Statistical Dogma While Establishing a Modern, Secure Distributed Data Management and Imaging Transport System: The Pediatric Brain Tumor Consortium Phase I Experience

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Abstract

The Pediatric Brain Tumor Consortium (PBTC) is a multidisciplinary cooperative research organization devoted to the study of correlative tumor biology and new therapies for primary central nervous system (CNS) tumors of childhood. The PBTC was created in 1999 to conduct early-phase studies in a rapid fashion in order to provide sound scientific foundation for the Children's Oncology Group to conduct definitive trials. The Operations and Biostatistics Center (OBC) of the PBTC is responsible for centrally administering study design and trial development, study conduct and monitoring, data collection and management as well as various regulatory and compliance processes. The phase I designs utilized for the consortium trials have accommodated challenges unique to pediatric trials such as body surface area (BSA)-based dosing in the absence of pediatric formulations of oral agents. Further during the past decade, the OBC has developed and implemented a state-of-the-art secure and efficient internet-based paperless distributed data management system. Additional web-based systems are also in place for tracking and distributing correlative study data as well as neuroimaging files. These systems enable effective communications among the members of the consortium and facilitate the conduct and timely reporting of multi-institutional early-phase clinical trials.

Keywords: pediatric oncology, computing and operational infrastructure, early phase clinical trials, paperless data acquisition and management

Introduction

The Pediatric Brain Tumor Consortium (PBTC) (www.pbtc.org) was initially funded by the NCI in 1999 as a multidisciplinary cooperative research organization devoted to the study of correlative tumor biology and new therapies for primary central nervous system (CNS) tumors of childhood. The PBTC's mission is to contribute rapidly and effectively to the understanding and cure of these tumors through the conduct of multicenter, multidisciplinary, innovative studies with designs and analyses based on uniformly high-quality statistical science. While the primary mission of the PBTC is to identify through laboratory and clinical science superior treatment strategies for children with brain cancers, the PBTC investigators also recognize their profound responsibility to meet the special needs of the children and families as they face this enormous challenge. PBTC member institutions include most of the larger pediatric neuro-oncology centers, translational biology laboratories in pediatric CNS neoplasia, pediatric pharmacology programs including NCI's Pediatric Preclinical Testing Program, pediatric neurosurgical and radiation therapy centers, and pediatric neuroimaging programs. The member academic centers and children's hospitals diagnose and treat approximately 30% of children with primary brain tumors in the United States.

As indicated above, the PBTC's main objective is to develop and carry out novel phase I, phase II, and pilot trials of new cytotoxic and molecularly targeted therapies (MTAs or cell signaling agents), novel treatment delivery technologies, and radiation treatment strategies in children aged up to 21 years with primary CNS tumors. As part of this objective the consortium has invested substantial effort in identifying and studying direct or surrogate markers of brain tumors' responses to new therapies as well as conducting laboratory research on brain tumor specimens to further understand the biology of pediatric brain tumors. Another focus has been to develop and coordinate innovative neuroimaging techniques. The PBTC's Neuro-Imaging Center (NIC), co-housed at the PBTC's Operations and Biostatistics Center (OBC) in Memphis, TN, and at Children's Hospital Boston, MA, was established in May 2000. To date the NIC has largely concentrated on research activities evaluating new treatment response criteria and understanding regional brain effects, including the study of significant neurotoxicity in developing children's central nervous system.

Figure 1 provides a schematic of the PBTC organizational chart. A key component of the PBTC is its OBC. The OBC centrally administers many of the operational processes of the PBTC including data collection from participating institutions and laboratories using a secure electronic data transfer system. The OBC, under the direction of the Executive Director and with oversight by the PBTC Chair and Steering Committee, is responsible for coordinating concept review and scoring, protocol development, protocol amendments/status changes, study conduct, study monitoring, data management, quality control/assurance, regulatory compliance, on-site audits, PBTC semiannual meetings, performance monitoring, managing the fiscal affairs of the PBTC, and statistical design and analysis of trials and studies.

The following sections discuss in more detail the electronic communications and data-sharing infrastructure, operational procedures for patient registration, and data acquisition during phase I trials as well as statistical designs and analyses employed. The article concludes with a brief discussion.

Electronic Communications and Data Acquisition Infrastructure

The OBC is responsible for establishing electronic communication with member institutions to facilitate protocol development and

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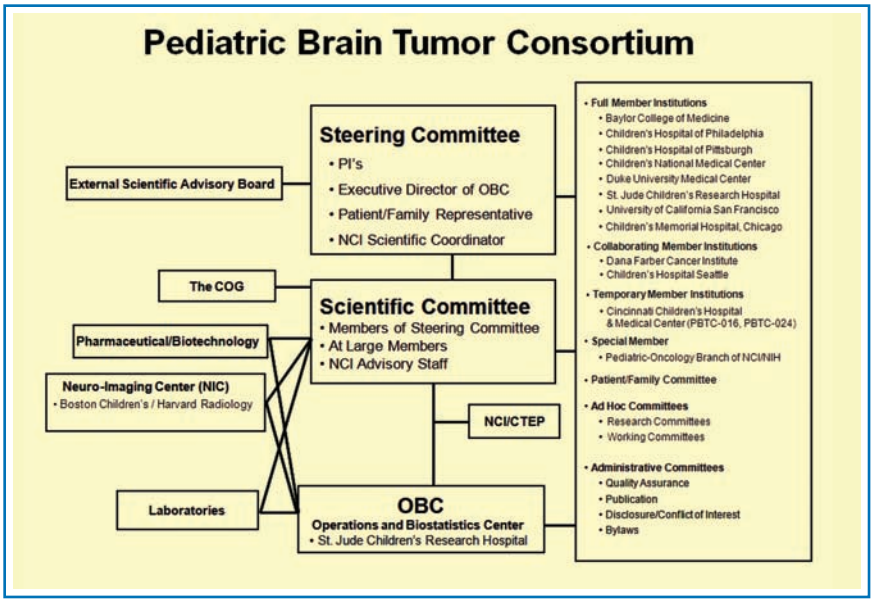

Figure 1. PBTC organizational chart.

study monitoring, as well as aiding in the activities of protocol, scientific and administrative committees. The OBC infrastructure supports communication among the PBTC member institutions, PBTC-NIC, Quality Assurance Review Center, PBTC laboratories, and central reviewers. Relevant communication methods include web site postings, e-mail (containing no patient-specific data), teleconferences, and videoconferences. Secure virtual private network (VPN) communications are used for data transfers between member institutions and the OBC; neuroimaging file transfers between member institutions and the OBC and between the OBC and the NIC component at Children's Hospital Boston; data transfers between the OBC and PBTC correlative laboratories; and data reporting, data sign-offs, and patient evaluation between the OBC, protocol study chairs, and monitoring committees.

The Consortium employs a paperless distributed data management infrastructure, which is illustrated in *Figure 2*. The site laptops are equipped with the CISCO VPN software client to connect securely to the OBC. The OBC has two multiprocessor-based high-end servers for the various patient databases, correlative laboratory database, image analysis database, other auxiliary databases, and for archiving neuroimaging data, which is illustrated in *Figure 3*. The database servers run Microsoft SQL Server and Microsoft Office suite for database needs and eFilm™ software for the neuroimaging DICOM data transfers. The OBC also provides File Transfer Protocol (FTP) service to the member institutions to facilitate database transfers and web services to access web-based forms for sites to submit requests and data to the OBC as well as to provide real-time data reports to PBTC investigators. We believe it is no longer necessary or desirable to rely on paper-based systems for data collection, data monitoring, reviewing and for storing regulatory documents, and informed consent forms. The driving principle of our evolving electronic infrastructure is to implement *data-driven human activity*. Hence, we strive to develop comprehensive computer systems to monitor and process accumulating data and to notify appropriate individuals when processing by a human is required. The OBC currently has one PhD and three MS-level computer scientists for design, implementation, and maintenance of these computer systems.

Patient registration/reservation, data entry, and data uploads to the OBC

Site clinical research associates (CRAs) use their local area network to connect to the internet and initiate a secure VPN connection to the OBC via the VPN client on their PBTC Windows-based laptops. They then use Internet Explorer to connect to the online patient registration system to register a patient, to reserve a slot or to be placed in the standby queue for a given PBTC protocol. If a slot is available and the site knows that a patient is eligible, then the patient may be registered. If eligibility remains to be confirmed then the slot can be reserved and the site has 7 days to register the patient. Standby queues are maintained for all clinical trials when there are no available slots. At the time slots become available standbys are automatically elevated to reservation status based on their position in the queue. After registering a patient, the database program is initiated to retrieve the patient registration information into their replica database. This process of system-based complete patient registration—wherein the patient IDs are directly entered by the OBC server into the site's replica database—ensures total data integrity and an error-free system. Sites fax consent forms and other regulatory paperwork to the OBC using the fax server. Via Microsoft Exchange mail integration, the faxed documents are distributed within the OBC by e-mail to the appropriate protocol coordinator (PC) and are also archived as net-based documents, which are used as hyperlinks in the consortium databases for easy, electronic access by OBC staff.

Sites are required to upload the data file to the OBC at least once a week to ensure data backup and are encouraged to upload data as it is entered. Uploaded database replicas are synchronized several times a day to generate the PBTC-centralized hub database that provides data on a real-time basis for the various web-based data reports. The hub database is also loaded into the SQL server back-end database in the OBC to enable the PCs to monitor changes made to the data in essentially real time.

When the PBTC started in 1999, not all member sites had fully functional, high-speed internet as well as wireless networking capability. Hence, we opted to set up the main clinical database, *PedBraTum* in Microsoft Access, providing for site-specific databases to be complete as described above. During the second grant period that resumed in 2004, the PBTC computing staff developed both the *ProtoLab* system that captures all the correlative data including pharmacokinetics, pharmacodynamics, and neuropathology data from the various correlative laboratories and the *Image Analysis* database that captures imaging parameters from the NIC at Children's Hospital Boston, and unlike *PedBraTum*, these are web-based, secure, remote data entry systems. Today, all eight PBTC sites have high-speed internet as well as wireless networking capability. During the next 5 years, *PedBraTum* will also become a web-based system with secure, remote data entry capability.

Procedures for Data Transmittal, Editing, and Quality Control/Verification

There are required procedures and assurances for assessing patient eligibility, evaluability for dose finding as well as toxicity outcome

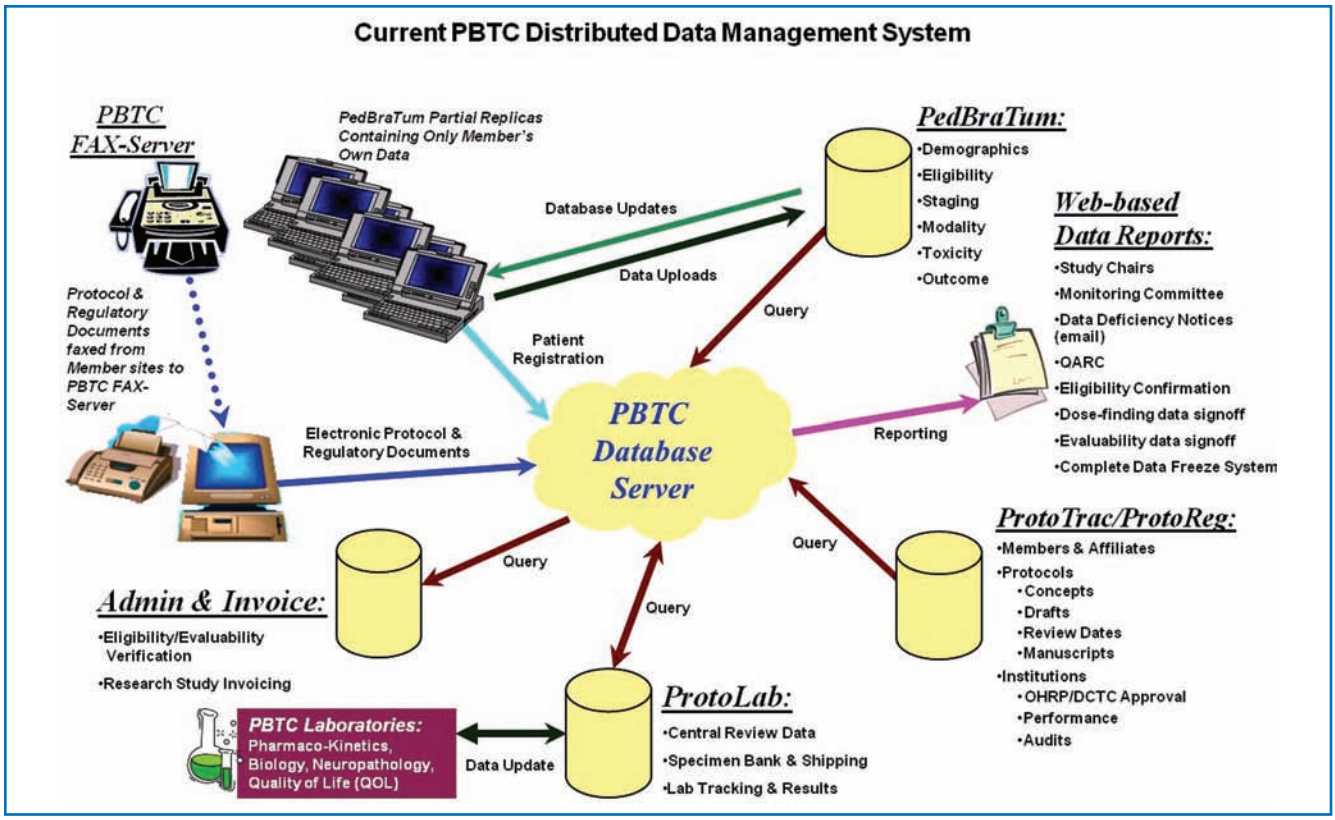

Figure 2. Current PBTC distributed data management system.

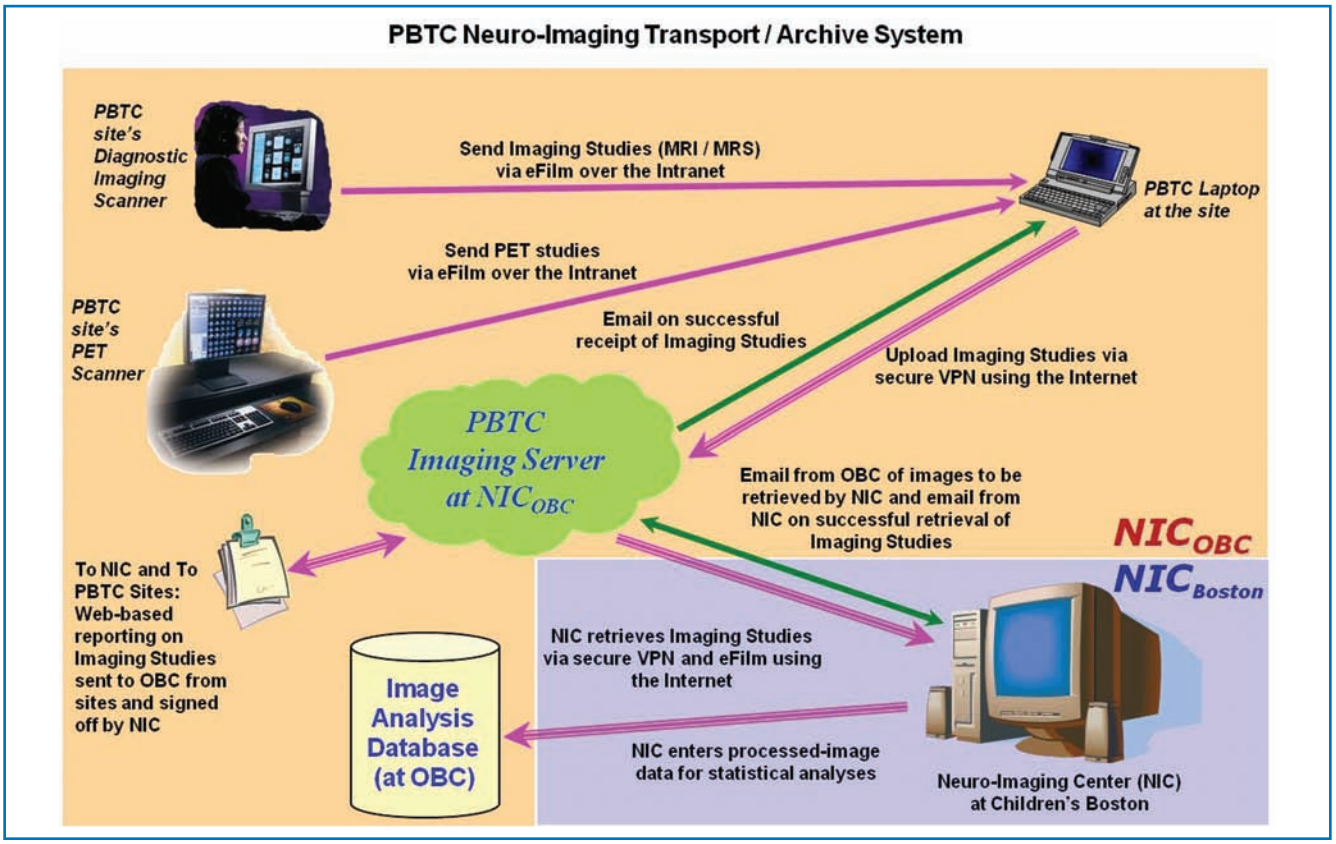

Figure 3. PBTC neuroimaging transport/archive system.

in phase I trials that need to be followed within prespecified timelines. When a patient is registered or the dose-finding period has been completed, the site CRA has two working days to complete and upload the required data to the OBC. Note that site CRAs are expected to upload these accumulating data weekly during treatment courses and the OBC PCs review these accumulating data daily for completeness, which leads to regular data queries that are generated as necessary to the site CRA. Only investigators and CRAs at a given PBTC site have authority to change data submitted for patients treated at their site. The site CRA and responsible OBC PC have eight additional working days to ensure that the data are complete, consistent, and ready for investigator review. At the end of this step, the data are "locked" and cannot be changed without a formal request to initiate OBC "unlocking" procedures. The locked data are then provided to the patient's attending physician (AP) with the OBC PC's assessment of whether the patient is eligible for the study or evaluable for the dose-finding objective. The AP must electronically sign that the data are complete and accurate as well as signify whether they agree with the OBC PC's assessment. The data are then provided to the protocol study chair (PSC) who is required to review and confirm that the data are accurately interpreted per protocol by electronic "sign-off" resulting in the final evaluation status. Both the AP and the PSC may send queries back to the OBC PC, requesting clarification or additional information in order to be able to sign-off. The same procedures are used for AP and PSC reviews and sign-offs of all protocol data as patients complete each course of therapy. The prospective data review and sign-off not only provides quality control of our data in terms of verification by the AP and interpretation by the PSC but also allows us to promptly identify and correct inaccurate and missing information and ensure timely publication of protocol findings. Furthermore, our main clinical database maintains a complete auditing trail of all modifications of submitted data. The close interaction of site CRA, OBC protocol coordinator, AP, and PSC provides quality control of our data in terms of verification by the AP and interpretation by the PSC. The on-site audits that are conducted at least once every 2 years also provide an alternative means for data verification and completeness.

Assigning drug dose levels during phase I trials

Following the PSC affirming evaluability of a patient that had completed the dose-finding period of a phase I trial and signing-off on the assessment of whether the patient experienced a DLT as defined by the protocol, an automatic e-mail is generated to notify the statistical team so that a recommendation regarding the next step in the trial can be communicated to the PSC. The decisions include dose escalation or de-escalation for the next cohort of patients or declaring the maximum tolerated dose (MTD) as estimated or expanding the cohort at the current dose. If the design is traditional, then the review and recommendation is simpler but nevertheless requires review by at least two statisticians before a recommendation is made to the PSC. If the trial uses the continual reassessment method (CRM)[1,2] for dose finding, then at least two independent calculations of the CRM-estimated MTD are required by the team of statisticians who review the data and the associated model estimates. Following a consensus the designated study statistician forwards the recommendation to the PSC for approval.

There are currently three PhD and three MS-level statisticians who are part of the OBC staff, though none are assigned full-time to the OBC. All six statisticians have access to the dose-finding data for all PBTC phase I trials that can be accessed on trial-specific password-protected, internal web pages, called the DLT monitoring pages. These pages are populated automatically once the relevant data are entered in the databases and are signed off by the PSC. The DLT monitoring pages not only provide easy and secure access to the data but also contain all the relevant information needed for dose escalation/de-escalation decisions for all patients who have been enrolled on the trial, for example, eligibility and evaluability status, assigned and body surface area (BSA)-adjusted actual dose, and DLT outcome. Hence, it is rare that the statistical review of assigning a dose to the next cohort of patients is not completed within a few hours of the triggering e-mail and never longer than a day.

Phase I Clinical Trials: Designs and Analyses

For PBTC dose-finding clinical trials, the MTD of a therapeutic regimen is typically selected from a prespecified set of doses. The approach employed to estimate the MTD is one of two types of designs: (1) a modified version of the CRM or (2) the traditional dose escalation, also known as the 3 + 3 empirical design. The CRM is the preferred approach for many of the PBTC trials because of its favorable operating characteristics[2] and because of its ability to incorporate specific problems encountered in the MTD estimation such as lack of a pediatric formulation, missed DLTs, and dosing errors. We use the traditional design mostly for lead-in assessments of one or two doses that do not require estimating an MTD or when other constraints require it.

Table 1 lists the 17 phase I trials that have been conducted to date by the PBTC. Most of these trials are complete and have been published while others are currently active. Stratification was employed in 7 of the 17 (41.18%) phase I trials, and in 12 studies (70.58%) CRM was the dose-finding algorithm.

A significant proportion of the phase I agents/regiments tested within the PBTC have been oral and many do not have a pediatric formulation (e.g., PBTC-003, PBTC-020, and PBTC-023). Since oral agents are typically dosed in children based on BSA, lack of a pediatric formulation may result in large discrepancies between the closest deliverable dose and the targeted dose to which patients are assigned. For PBTC-006[8], for example, *Figure 4* shows the relationship between the assigned doses (horizontal lines) versus the actual deliverable dosages as a function of BSA (hatched lines). The overlapping hatched lines (also marked by the arcs on the figure) highlight areas of concern. For example, patients assigned to either 150 or 200 mg/m^2 with BSAs between 0.50 and 0.62 m^2 receive exactly the same dosage; thus, if one must "dose-reduce" due to toxicity observed at 200 mg/m^2 then patients assigned to 150 mg/m^2 with BSAs between 0.50 and 0.62m^2 would receive the same too-toxic dose. Furthermore, two patients assigned to 200 mg/m^2 can have a 38% difference at the same dose level: one with a BSA of 0.62 m^2 receives 238 mg/m^2 and another with a BSA of 0.87 m^2 receives 172 mg/m^2. Clearly, such cases raise safety concerns in the context of phase I trials. Thus, if the pediatric formulation limitations make it impossible to safely deliver the lower dose of the agent to patients in the target population, this would be taken into account. In the PBTC we have managed such safety concerns by restricting further accrual to patients with larger BSAs at the affected dose levels.

If, in fact, one of the affected dose levels is declared as the dose to be carried forward to a phase II study, it is, of course, possible that limiting accrual to patients with larger BSAs during

Protocol title	Agent type	Strata	Correlative studies	Statistical algorithm
PBTC-001: Pilot study of systemic and intrathecal chemotherapy followed by conformal radiation for infants with embryonal intracranial central nervous system tumors[3]	IT	No	PK, B	CRM
PBTC-002: A phase I study of SU5416 in pediatric patients with recurrent or progressive poor prognosis brain tumors[4]	MTA	EIACD	PK, B, NI	Traditional
PBTC-003: A phase I trial of escalating oral doses of SCH 66336 in pediatric patients with refractory or recurrent brain tumors[5]	MTA	No	PK, B	CRM
PBTC-004: A phase I study of intrathecal Spartaject™-busulfan in children with neoplastic meningitis[6]	IT	No	PK	CRM
PBTC-005: A phase I trial of temozolomide and O6-benzylguanine in pediatric patients with recurrent brain tumors[7]	Cytotox/MTA	Prior RT and G-CSF status	PK, B	CRM
PBTC-006: A phase I/II trial of STI571 in children with newly diagnosed poor prognosis brainstem gliomas and recurrent intracranial malignant gliomas[8]	MTA	Tumor type	PK, B, NI	CRM
PBTC-007: A phase I/II trial of ZD1839 (Iressa™) and radiation in pediatric patients newly diagnosed with brain stem tumors or incompletely resected supratentorial malignant gliomas with phase II limited to brain stem tumors	MTA	EIACD	PK, B, NI	Traditional
PBTC-012: A phase I study of Cilengitide (EMD 121974) in children with refractory brain tumors[9]	MTA	No	PK, B, NI	CRM
PBTC-014: A phase I/II trial of Zarnestra and XRT in pediatric patients with newly diagnosed nondisseminated intrinsic diffuse brainstem gliomas[10]	MTA/RS	No	PK, NI	Traditional
PBTC-016: A phase I molecular biology and phase II study of lapatinib (GW572016) in pediatric patients with recurrent or refractory medulloblastoma, malignant glioma, or ependymoma	Cytotox/BRM	CS	PK, PG, B	CRM
PBTC-017: A phase I study of Cloretazine™ (VNP4010M) in children with recurrent, progressive, or refractory primary brain tumors[11]	Cytotox	Prior therapy	PK, B	CRM
PBTC-018: A phase I trial of CC-5013 (lenalidomide) in pediatric patients with recurrent or refractory primary CNS tumors	MTA	No	PK, PG, NI, B	CRM
PBTC-019: A phase I pharmacokinetic optimal dosing study of intrathecal topotecan for children with neoplastic meningitis	IT	No	PK, B, NI	Traditional
PBTC-020: A phase I clinical trial of AZD2171 in children with recurrent or progressive CNS tumors	MTA	EIACD	PK, PG, B, NI	CRM
PBTC-021: A phase I trial of capecitabine rapidly disintegrating tablets and concomitant radiation therapy in children with newly diagnosed brainstem gliomas and high-grade gliomas	Cytotox/RS	No	PK, PD, NI	Traditional
PBTC-023: Phase I and pharmacokinetic study of enzastaurin (LY317615) in children and adolescents with refractory primary CNS tumors	MTA	No	PK, B, NI	CRM
PBTC-024: A phase I study of MK-0752 in pediatric patients with recurrent or refractory CNS malignancies	MTA	No	PK, PD, PG, B, NI	CRM

B = biology; CRM = continual reassessment method; CS = corticosteroids; cytotox/BRM = cytotoxic agent and biologic response modifier; EIACD = enzyme-inducing anticonvulsant drugs; G-CSF = granulocyte colony-stimulating factor; IT = intrathecal; MTA = molecularly targeted agent (including antiangiogenesis agents); NI = neuroimaging; PD = pharmacodymanics; PG = pharmacogenetics; PK = pharmacokinetics; RS = radiosensitizer; RT = radiation.

Table 1. Overview of PBTC phase I clinical trials.

the phase I trial may result in restrictions on eligibility for the phase II trial. This may encourage investigators to consider alternative dosing strategies for smaller patients such as dosing by weight during the phase I trial. Alternatively and perhaps more desirably, such potential restrictions have provided an added impetus for the company to make a pediatric formulation for the study in some cases. The issue for subsequent phase II trials is again one of assigned versus deliverable dosages. We have not yet designed a follow-up phase II trial when these restrictions were noted in the phase I investigation, but expect that it is only a matter of time. In the PBTC we would design the phase II trial by imposing the same restrictions based on BSA as were adapted in the phase I trial. The recommendation to apply these restrictions for subsequent phase II trials would be included in the published manuscript describing our phase I experience. It is also possible that a pediatric formulation would have become available by the time a phase II trial is initiated, thus eliminating the necessity for subsequent constraints.

While studying dose–toxicity relationships, the above-described variations from the targeted dose may significantly

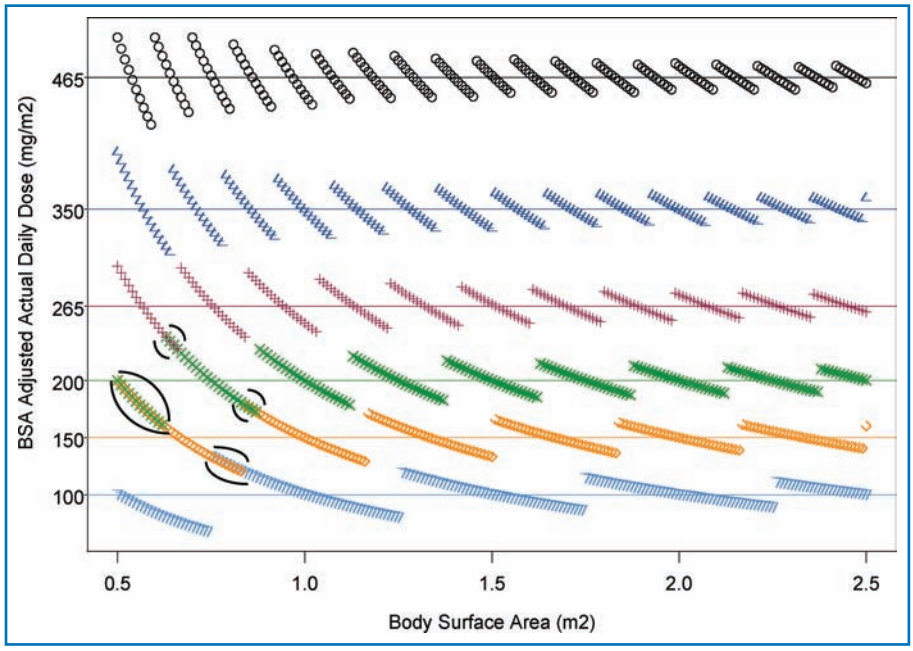

Figure 4. Variations from target doses: BSA-adjusted actual daily dose (mg/m^2) versus body surface area (m^2) for PBTC-006 (phase I trial of STI571 in children with newly diagnosed brainstem gliomas).

impact the MTD estimate. In phase I studies with no pediatric formulation, the use of the traditional design is thus questionable as the method assumes that the delivered doses are identical to the targeted doses, which clearly is not the case. As *Figure 4* also indicates, the discrepancies between the assigned and the actual dose are most notable for smaller patients, typically with BSAs less than 1 m^2, which represents approximately 45% of the PBTC patient population.

Although rarely reported in the literature, dosing errors or missed DLTs do occur during the conduct of phase I trials, and the PBTC is no exception. In the former case, rather than discarding the data from a miss-dosed patient, the CRM can incorporate the DLT outcome from such a case at the actual delivered dosage. Similarly in cases where missed DLTs are identified retrospectively, a reestimate of the MTD is needed. Such events may create difficulty in reinterpreting results for the 3 + 3 designs. For example, if the retrospective DLT is identified at a dose level that already had six patients and one DLT but the dose level above it was studied and found to be safe, it is not clear what the interpretation of the new DLT should be with respect to the MTD. Such a situation is not a problem for the CRM as the MTD is estimated using all data from all dose levels and thus the model would simply be rerun to estimate the MTD with the revised toxicity assessment. A third scenario where this property of the CRM has proved to be very useful was encountered in the context of a currently ongoing PBTC phase I trial, where late toxicities prompted the DSMB to recommend extending the dose-finding period from 4 to 6 weeks. This change led to two new DLTs being incorporated into the CRM model and were used in determining the starting dose of the amended trial.

Correlative study objectives

It should be noted that a fundamental difference with respect to correlative studies between pediatric and adult phase I trials is that participation in such studies is voluntary in the former. This option emanated from a 2002 workshop sponsored by the National Cancer Institute Cancer Therapy Evaluation Program that was composed of cancer patient advocates, pediatric and medical oncologists, bioethicists, and institutional review board members.[12] Since requiring participation in PK or correlative biology could be considered coercive (unless the results of these studies directly impact the treatment of the patient or the analysis of a primary study objective), the PBTC has followed a policy similar to that of other pediatric cooperative groups and advocated that participation in correlative studies should be optional. Despite the limitations of voluntary participation, the PBTC has routinely achieved adequate subject participation to meet secondary correlative study aims, which typically address PK, PD, biology, and imaging questions. This success has been substantially aided by protocol and correlative study-specific shipping accounts set up by the OBC that offer real-time tracking information and has been facilitated by the web-based correlative databases such as *ProtoLab*, which allow the laboratories to enter and retrieve data in a convenient fashion.

As *Table 1* clearly indicates, various correlative study questions are routinely integrated into the PBTC phase I trials. Not surprisingly all of our phase I trials involved a PK objective, 4/17 (23.5%) incorporated PG/PD endpoints, 14/17 (87.5%) and 11/17 (64.7%) integrated biology and neuroimaging objectives, respectively. Although we have demonstrated the feasibility of collecting adequate correlative data/specimens/images to address these secondary objectives, we have also encountered various challenges. Naturally, small sample sizes are expected from studies that rely on voluntary components of a pediatric phase I trial, but it is also the case that some sites have more strict regulations regarding research procedures such as PET scans, frequency, and amount of blood draws, further decreasing the sample size available for correlative studies. In addition, our experience indicates that approximately 70% of patients who participate in our phase I trials are off treatment within the first two courses. Hence, objectives that involve collection of data beyond course 2 are often infeasible. Further, since pre-treatment specimens are often needed in order to properly analyze and interpret the post-treatment measures in such small sample settings, unless pre-treatment specimens/images are obtained from a patient, collecting post-treatment correlative information is discouraged.

Despite the fact that each phase I trial provides a relatively small number of patients from whom correlative data is available, the PBTC is well positioned to run cross-protocol analyses since the consortium has studied agents with similar mechanisms of action (e.g., antiangiogenic agents) in the same patient population almost simultaneously or in close succession. Such cross-protocol analyses, which are currently in progress, would have more power and may provide additional information to help formulate hypotheses that can be prospectively tested in future trials.

Discussion/Conclusions

The PBTC represents a closely coordinated clinical research trials group focused on multidisciplinary investigations in the challenging area of pediatric brain tumors. During the past decade, through scientists based in member institutions, contacts with the NCI and pharmaceutical companies and interactions with the predecessor consortia of the new Adult Brain Tumor Consortium, the PBTC has aimed to identify and translate innovative therapies from the laboratory to early-phase clinical testing. As indicated above, one of our major foci has been on the molecularly targeted agents. These PBTC trials have often served as the initial phase I experience of these agents in children. The phase I designs utilized for the consortium trials have accommodated challenges unique to pediatric trials such as BSA-based dosing in the absence of pediatric formulations of oral agents as well as optional participation in correlative studies. In disease categories where outcome has lagged behind other types of childhood cancer (e.g., brainstem gliomas, malignant gliomas, infant embryonal tumors, refractory medulloblastomas, and ependymomas), we have introduced molecularly targeted studies with novel trial designs to (1) assess the presence of the target in patient-specific tissue (where possible), (2) test the ability of the agent to downregulate the signaling target, and (3) correlate findings with response to the molecular antagonist. The consortium has systematically studied the pharmacokinetics of new agents in childhood brain tumors, selectively analyzing pharmacodynamics and pharmacogenomics. With its unique resources and collective expertise, the PBTC is well positioned to generate valuable knowledge via translational science that can be carried forward to more definitive trials.

As outlined in the previous sections, the consortium has also developed various operational procedures as well as a data acquisition/storage and communication infrastructure that may serve as a model for other consortia. The OBC has designed, developed, implemented, and maintains a state-of-the-art secure internet-based paperless distributed data management system that is efficient and has effectively supported every PBTC protocol developed to date. Additional web-based systems are also in place for collecting, anonymizing, storing, and distributing neuroimaging files as well as for tracking specimen, tissue and slide collection, submission, and processing. These systems facilitate effective communications among the members of the consortium. The OBC has also demonstrated that fully electronic and secure, distributed data management and neuroimaging transport systems are not only technically feasible but as implemented, will facilitate the conduct and timely reporting of multi-institutional early-phase clinical trials.

Acknowledgments

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